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10/018,373	12/06/2001	Hans Bigalke	Merz 32 PCT US/dln	4496

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,373	BIGALKE ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's response filed July 27, 2005 is acknowledged. Claims 1-10 have been cancelled. The Examiner did not include rejections of pending claims 16-18 in the last Office action. For clarification of the record, claims 11-18 are pending and under examination. New rejections are set forth below. This Office action is Non-Final.

Rejections Withdrawn

2. In view of Applicant's remarks the following rejections are withdrawn.

a) rejection of claims 11-12 under 35 U.S.C. 103(a), pages 2-5, paragraph 3, of the previous Office action.

b) rejection of claims 11-13 under 35 U.S.C. 103(a), pages 5-7, paragraph 4, of the previous Office action.

c) rejection of claims 11-12 and 14-15 under 35 U.S.C. 103(a), pages 7-10, paragraph 5, of the previous Office action.

d) rejection of claims 11-12 and 14-15 under 35 U.S.C. 103(a), pages 10-12, paragraph 6, of the previous Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

3. Claims 11-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a human or animal with cosmetic conditions, dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin comprising administering a 145 to 200 units of pure botulinum toxin to the human or animal a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes does not enable administering doses of about 2500 units and above of botulinum toxin in a method for treating a human with cosmetic condition, dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It should be noted that the instantly claimed invention encompasses all serotypes of botulinum toxins, at any dosage as well as encompassing botulinum toxins prepared by any manufacture. The specification provides working examples that disclose a method of treating spasmodic torticollis and cerebral palsy comprising administering to a patient 145 units and 200 units, respectively (Examples 7-8).

The instant specification has failed to provide enablement for cosmetic conditions, dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin comprising administering amounts of pure botulinum toxin ranging from 2500 units and above) to the human.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The state of the art regarding botulinum toxin administration to subjects (humans) is cited below.

Gil et al *(U.S. Patent No. 6,787,517 published September 7, 2004)* teach that botulinum toxin is the most lethal natural biological agent known to man and has a very

potent LD_{50} (column 2). Gil et al teach that a specific dose of a toxin that would be lethal to 50% of the population of a certain species of an animal is called the LD_{50} (column 2). Gil et al teach that the estimated LD_{50} of botulinum toxin A (available from Allergan, Inc., BOTOX®) in humans is about 150,000 picograms or about 3000 units (column 2). Carruthers et al *(U.S. Patent No. 6,358, 917 B1 published March 19, 2002)* teach that botulinum toxin (BTX) is administered in units (column 3). Carruthers et al teach that "unit equivalents" is an amount of botulinum toxin which is equivalent to standard units of botulinum toxin A (column 3). Carruthers et al teach that a standard unit of BTX-A is defined as the L_{50} for female Swiss Webster mice weighing 18-20 grams (column 3). Carruthers et al teach that the estimated human LD_{50} (for a 70-kg person is 40 units/kg or about 2500-3000 units (column 3).

It should be noted that the instant claims do not recite any particular dosage. The prior art has taught that administering 2500-3000 units of botulinum toxin would result in death to a human patient. Thus, the instant specification has failed to teach the skilled artisan to make and use the claimed invention. It should be noted that *Webster's II New Riverside University Dictionary, The Riverside Publishing Company, 1984* defines the word "treat" as a matter of giving medical aid. The skilled artisan would conclude that administering a compound to a patient the would result in death would not be a defined as treating the patient. Thus, it would require guidance to determine the dosages the skilled artisan could administer to a patient to practice (make and use) the claimed method. Therefore, the instant specification has failed to teach how to make and use the invention commensurate in scope with these claims.

In view of all of the above, Applicant has not satisfied the requirements as set forth under 35 U.S.C. 112 first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 11-18 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 11-18 recite "..."wherein the neurotoxin or mixture of neurotoxins is free of complexing proteins which naturally form complexes with botulinum neurotoxins". It is unclear as to what Applicant intends. Does Applicant intend that the botulinum neurotoxins are purified? Clarification and/or correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It should be noted the Examiner is viewing the claim limitation "wherein the neurotoxin or mixture of neurotoxins is free of complexing proteins which naturally form complexes with botulinum neurotoxins" as being the same as a purified neurotoxin since the specification has not specifically defined the phrase "free of complexing proteins". It should be noted that the specification discloses purified botulinum toxin A and B (see Examples 1-3). The method of using the purified botulinum toxins are disclosed in Examples 7-8 of the instant specification.

5. Claims 16-18 are rejected under 35 U.S.C. 102(b) as anticipated by Green et al *(Movement Disorders, Vol. 8, No. 4, 1993, p. 479-483).*

The claims are drawn to a method of treating a human or animal with dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin comprising administering to the human or animal a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Green et al teach a method of treating patients (humans) with torticollis with immunity to botulinum toxin type A (see the Abstract and the Title). Green et al teach that patients that have an immunity to botulinum toxin A were successfully treated with botulinum toxin F (see the Abstract and page 480). Green et al teach that the botulinum toxin F administered to patients was purified (page 480). Green et al anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11-12 and 14-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Green et al *(Movement Disorders, Vol. 8, No. 4, 1993, p. 479-483)* in view of Carruthers et al *(Basic and Clinical Dermatology, Marcel Dekker, Inc, New York, Chapter 11, pages 207-236).*

The claims are drawn to a method of treating a human or animal cosmetic condition treatable with a botulinum toxin neurotoxin comprising administering to the human or animal a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Green et al teach a method of treating patients (humans) with torticollis with immunity to botulinum toxin type A (see the Abstract and the Title). Green et al teach that patients that have an immunity to botulinum toxin A were successfully treated with

botulinum toxin F (see the Abstract and page 480). Green et al teach that the botulinum toxin F administered to patients was purified (page 480).

Green et al do not teach treatment of cosmetic conditions.

Carruthers et al teach that botulinum neurotoxin type A (botulinum A exotoxin) can be used for cosmetic conditions such as glabellar wrinkles or lines, Crow's feet, horizontal forehead lines, neck lines , mental creases , melolabial folds and facial asymmetry (pages 216-230). Carruthers et al suggest that other botulinum neurotoxins can be used as alternative treatments for individuals who have developed antibodies to botulinum toxin type A and have become non-response to that treatment (page 208).

It would have been *prima facie* obvious at the time the invention was made to administer purified botulinum toxin type F to patients that have developed neutralizing antibodies to botulinum neurotoxin type A and are nonresponsive to botulinum neurotoxin A therapy because Carruthers et al suggest that other botulinum neurotoxins can be used as alternative treatments for individuals who have developed antibodies to botulinum toxin type A and Green et al has demonstrated that patients that are non-responsive to treatment with botulinum neurotoxin A are responsive to treatment with purified botulinum neurotoxin type F. It would be expected barring evidence to the contrary, that botulinum toxin neurotoxin A can be used as an alternative to treat patient that have immunity to botulinum neurotoxin A therapy. The combination of prior art references teach the claimed invention.

7. Claim 13 is rejected under 35 U.S.C. 103(a) as unpatentable over Green et al and Carruthers et al as applied to claims 11-2 and 14-15 above and further in view of Shelley et al (*Journal of the American Academy of Dermatology, February 1998, pages 227-229).*

The claims are drawn to a method of treating a human or animal cosmetic condition treatable with a botulinum toxin neurotoxin comprising administering to the human or animal a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes and wherein the cosmetic condition is hyperhidrosis.

The teachings of Green et al and Carruthers et al have been described previously.

Green et al and Carruthers et al do not teach hyperhidrosis.

Shelley et al teach that palmar hyperhidrosis can cause serious social, psychologic and occupational problems (page 227). Shelley et al teach that botulinum toxin can be a safe and effective treatment for palmar hyperhidrosis (See the Abstract).

It would have been *prima facie* obvious at the time the invention was made to administer purified botulinum toxin type F to patients that have developed neutralizing antibodies to botulinum neurotoxin type A and are nonresponsive to botulinum neurotoxin A therapy as taught by Green et al and Carruthers et al because Carruthers

et al suggest that other botulinum neurotoxins can be used as alternative treatments for individuals who have developed antibodies to botulinum toxin type A and Green et al has demonstrated that patients that are non-responsive to treatment with botulinum neurotoxin A are responsive to treatment with purified botulinum neurotoxin type F. It would be expected barring evidence to the contrary, that botulinum toxin neurotoxin F can be used as an alternative to treat patients that have hyperhidrosis that have immunity to botulinum neurotoxin A therapy. The combination of prior art references teach the claimed invention.

Status of Claims

8. No claims allowed.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
July 20, 2006

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PRIMARY EXAMINER